REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 13, 14, 19-27, 31, 32, 34 and 36-38 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 12, 15-18 and 35 have been rejected under 35 U.S.C. §112, second paragraph, and 35 U.S.C. §101. This rejection is obviated by the cancellation of rejected claims 12, 15-18 and 35 without prejudice.

Claims 12, 15-18 and 35 have been rejected under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over Koenig et al. These prior art rejections are also made moot by the cancellation of rejected claims 12, 15-18 and 35 without prejudice.

Claims 12-27, 31, 32 and 34-39 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Ochoa et al. (U.S. Patent 5,296,353) in view of Babbit et al. (U.S. Patent 5,766,920), Ochoa et al. (U.S. Patent 5,443,983), Wallace et al., Santamaria et al., and Sekine et al. This rejection is respectfully traversed.

At column 3, lines 32-50, Ochoa '353 discloses in the background of the invention an example in which lymphocytes are stimulated by anti-CD3 antibody (soluble or solid phase bound) and IL-2 in order to obtain T-activated killer cells. However, when column 7, lines 54-68 and column 8, lines 1-35 are read carefully, they would suggest to one of ordinary skill in the art that because a side effect such as pulmonary toxicity results when lymphocytes are stimulated by IL-2, this side effect can be suppressed by (1) being stimulated with anti-CD3 antibody, (2) administering a small quantity of lymphocytes stimulated with anti-CD3 antibody to a living body and then administering IL-2. As Ochoa '353 indicates that it is possible to propagate lymphocytes in the living body, Ochoa '353 clearly indicates that it is not preferred to culture lymphocytes *in vitro* with anti-CD3 antibody and IL-2 at the same time.

The specification from line 36 in column 8 to line 2 in column 9 teaches that stimulation by only anti-CD3 antibody is desirable and that administration of IL-2 is most suitable on the seventh day of cultivation after stimulation by anti-CD3 antibody in case it is desired to administer IL-2 to the living body after administration of lymphocytes or during cultivation.

In the field of adoptive immunotherapy, the presently claimed invention relates to a method for stimulating lymphocytes derived from a virally infected patient in a culture medium which contains solid phase anti-CD3 antibody and IL-2. The lymphocytes are thus activated and then administered to a patient in order to treat the viral infection. However, as discussed above, Ochoa '353 denies the *in vitro* activation of lymphocytes under coexistence of anti-CD3 antibody and IL-2.

The examiner indicates that a method for activating autologous T-lymphocytes stimulated with OKT3 and IL-2 is disclosed in Babbit et al. However, when the relationships between anti-CD3 antibody and IL-2 as taught in Ochoa '353 and Babbit are considered together, this combination of teachings serves only to confuse a person of ordinary skill in the art.

The examiner also asserts that Ochoa, US Patent 5,443,983, shows an example in which LAK activated with anti-CD3 antibody and IL-2 is administered into an AIDS patient, but Ochoa '983 discloses that normal lymphocytes from an AIDS patient's twin brother are activated and these activated normal lymphocytes are administered to the twin brother who has AIDS. The purpose in Ochoa '983 is to determine whether or not a side effect is present when activated normal lymphocytes are administered to an AIDS patient. Since the

object of Ochoa '983 is completely different from that of Ochoa '353, then even if the disclosures were to be combined, there is no assurance that the combination would lead to activated lymphocytes derived from the viral infected patient and then administration of activated lymphocytes to the patient that is the object of the present invention.

The examiner further states that Wallace teaches IL-2 activation of T-cell precursors collected from the circulation of seropositive individual. As is clear from a carefully reading of the abstract, Wallace reports that such a cell line dependent on IL-2 is established by challenging with autologous EBV transformed cells that are obtained from the circulation of seropositive individuals, or in other words, a method for establishing general antigen-specific T cells. Therefore, Wallace does not provide any disclosure whatsoever that would indicate that Wallace's method can be used in adoptive immunotherapy. Moreover, because establishing cell lines is completely different from the field of adoptive immunotherapy, there is nothing obvious about combining Wallace with Ochoa or Babbit. Autologous EBV-transformed cells are used as an antigen in order to obtain a cell line specific to EBV. This is completely different from the anti-CD3 antibody stimulation in the present invention. Even if Wallace's method is combined with Ochoa '353, which applicant

emphatically deny is likely, they would not teach the presently claimed invention.

Next, the examiner argues that the long term-growth of antigen specific T-cell lines are induced by stimulating PBMC of a CMV patient with anti-CD3 antibody and IL-2 in Santamaria. The purpose of Santamaria, however, which is clear from the abstract, is to cultivate antigen specific T-cell lines in a system without feeder cells or a specific antigen. Santamaria nowhere teaches that it is possible to use the method for adoptive immunotherapy. On the other hand, lymphocytes are activated with anti-CD3 antibody in Ochoa '353 and Ochoa discloses that it is preferred that cultivation is for no more than 24 hours. Therefore, Ochoa's purpose is completely different from that of Santamaria. There is absolutely no motivation for one of ordinary skill in the art to combine two such different references.

Finally, though the examiner cites and applies the Sekine reference, which is applicant's own publication, Sekine in fact discloses a method for treating cancer patients where lymphocytes are stimulated with anti-CD3 antibody and IL-2 at the same time. Sekine is different from Ochoa '353 in purpose, in its method and in the subject for therapy. The only point in common between the two is merely the use of T cells. Accordingly, it would be difficult to combine the

different methods of Ochoa '353 and Sekine. Even if they were to be combined, because the methods are so different, this would only serve to confuse one of ordinary skill in the art.

The examiner states it in the third paragraph of page 7 in the Office Action that the applicant recognizes "T-cells and NK cells, can be activated and stimulated by IL-2 and that lymphocytes can be activated and stimulated with IL-2, with or without CD3 antibodies, including against viruses". However, the lymphocytes used in the passage of the present specification cited by the examiner are lymphocytes derived from a donor, but not lymphocytes derived from a viral infected patient. A first reference shows that lymphocytes derived from a donor are stimulated with IL-2, and EBV transformed donor lymphocytes, where, even in lymphocytes participating EBV to bone marrow transplantation, their propagation becomes possible. The next reference shows that lymphocytes derived from a donor are stimulated with anti-CD3 antibody, IL-2 and CMV infected fibroblast, and are effective for CMV therapy. While it is a common sense in immunology to achieve a therapeutic effect for CMV by using CMV specific T-cells, the present invention is directed to activating lymphocytes derived from a viral infected patient with anti-CD3 antibody and IL-2 and is a pioneering invention which does not require stimulation with other antigens.

The examiner's use of six different references with different purposes to put together this rejection appears to involves impermissible hindsight reconstruction. As discussed above, one of ordinary skill in the art would simply not be motivated to combine the disparate disclosures and teachings from such a large number of different references.

Accordingly, the combination of Ochoa '353, Babbit, Ochoa '983, Wallace, Santamaria and Sekine simply cannot lead one of ordinary skill in the art to the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /ACY/
Allen C. Yun
Registration No. 37,971

ACY:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\K\koui\Sekine1\pto\2007-02-15AMD_FINAL.doc